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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/595,682	06/16/2000	Mary K. Danks	SJ-0005	1625

31949 7590 04/09/2003

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	25

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/595,682	DANKS ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-14 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 12-14 and 18 are pending in the application.

This Office Action is in response to the Amendment filed on 11/18/02.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/18/02 has been entered.

Response to Amendment

Acknowledgment is made of Applicants' submission of Declaration on 11/18/02.

The rejection of claims 12-14 and 18 under 35 U.S.C. 112 first paragraph enablement has been changed to scope of enablement in light of Applicants' amendment of the claims.

Claims 12-14 and 18 are rejected under 35 U.S.C.112 first paragraph (written description) for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-14 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for sensitizing tumor cells to chemotherapeutic prodrug APC or CPT-11 *in vitro*, comprising transfecting tumor cells with a composition comprising an isolated polynucleotide encoding the rabbit carboxylesterase operably linked to a promoter directs specific expression of said carboxylesterase in said tumor cells, wherein expression of said carboxylesterase renders the tumor cells more susceptible to the cytotoxic effect of said chemotherapeutic drug; a method of inhibiting tumor cell growth *in vitro*, comprising sensitizing tumor cells by transfecting tumor cells with a composition comprising an isolated polynucleotide encoding the rabbit carboxylesterase operably linked to a promoter directs specific expression of said carboxylesterase in said tumor cells, contacting said tumor cells with chemotherapeutic prodrug APC or CPT-11 so that the tumor growth is inhibited; said methods while applied *in vivo*, wherein the polynucleotide encoding the rabbit carboxylesterase is carried by an adenoviral vector which is administered intratumorally or intravenously, and the chemotherapeutic drug is administered intravenously, does not reasonably provide enablement for such method for in vivo application, wherein the polynucleotide encodes any carboxylesterase, and the said enzyme and chemotherapeutic drug are delivered by any route. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In response to the enablement rejection, Applicants argue that a number of references cited by Applicants in the previous amendment and current amendment demonstrate the effectiveness of gene therapy in cancer treatment. Applicants further cite *In re Brana* and *Nelson v. Bowler*, and assert that the animal xenograft model described in the present application teaches

potential usefulness of this class of prodrugs metabolizing carboxyesterase in human. Applicants assert that the Examiner fails to provide evidence showing that one of ordinary skill or art would doubt the asserted utility. Applicants further submit a declaration that demonstrates intratumoral and intravenous administration of the recombinant adenovirus are suitable delivery methods for the claimed invention. Applicants assert that the specification supports the claimed invention to its full scope.

The above arguments have been fully considered but deemed unpersuasive. The instant specification only supports the claimed invention for *in vitro* but not in an *in vivo* setting over the full scope (see detailed discussion in the previous office action). *In re Brana* is applied improperly in this situation because the invention of *In re Brana* is a group of chemical compound, and the court decision is based on whether this class of compounds has practical utility *in vivo*. The animal model is considered to be sufficient in testing those chemical compounds because "the purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. *In re Jolles*, 628 F.2d at 1327, 206 USPQ at 890. Modern science has previously identified numerous successful chemotherapeutic agents." However, in the instant application, Applicants are claiming a method of sensitizing tumor cells and a method of inhibiting tumor growth both *in vitro* and *in vivo* by administering a nucleic acid encoding a carboxylesterase which can activate chemotherapeutic prodrug APC or CPT-11. The claimed method may have potential utility in human, the problem is whether the method can be practiced to its full scope without undue experimentation. The art of gene therapy as whole is considered unpredictable for reasons discussed in the previous office action. Therefore, the case law of *In re Brana* is not particularly

relevant for the current situation. Likewise, *Nelson v. Bowler* addresses the issue whether an *in vivo* test of chemical pharmacological compounds have practical utility. It is not relevant to the current situation. Applicants misconstrue the Examiner's position that the asserted utility of the method is in doubt, in fact, the Examiner only concerns whether the method can be practiced to its full scope without undue experimentation. This is a question of enablement, not utility.

The Declaration filed on 11/18/02 has been fully considered. The Declaration has demonstrated that intravenous or intratumoral injection to nude mouse carrying xenografts adenovirus carrying the rabbit carboxylesterase renders the tumor cells more sensitive to the chemotherapeutic agent CPT-11. The Declaration further demonstrated that such effect is achieved by increasing intracellular level of active metabolites SN-38 due to carboxylesterase activity. Considering the data presented in the instant specification and the Declaration, they support the enablement of a method for sensitizing tumor cells to chemotherapeutic prodrug APC or CPT-11 *in vitro*, comprising transfecting tumor cells with a composition comprising an isolated polynucleotide encoding the rabbit carboxylesterase operably linked to a promoter directs specific expression of said carboxylesterase in said tumor cells, wherein expression of said carboxylesterase renders the tumor cells more susceptible to the cytotoxic effect of said chemotherapeutic drug; a method of inhibiting tumor cell growth *in vitro*, comprising sensitizing tumor cells by transfecting tumor cells with a composition comprising an isolated polynucleotide encoding the rabbit carboxylesterase operably linked to a promoter directs specific expression of said carboxylesterase in said tumor cells, contacting said tumor cells with chemotherapeutic prodrug APC or CPT-11 so that the tumor growth is inhibited; and said methods while applied *in vivo*, wherein the polynucleotide encoding the rabbit carboxylesterase is carried by an

adenoviral vector which is administered intratumorally or intravenously, and the chemotherapeutic drug is administered intravenously. However, these data is not sufficient to support the claimed method *in vivo*, wherein the nucleic acid encoding the rabbit carboxylesterase is delivered by any route. All the references cited by Applicants do not teach the effectiveness of gene therapy beyond intratumoral delivery. These data also fails to enable such method wherein the nucleic acid encodes any carboxylesterase, and co-administration of any chemotherapeutic prodrug. The unpredictability of the claimed method using any carboxylesterase and chemotherapeutic drug was discussed in the previous office actions. Therefore, the claims are only enabled to the scope discussed above.

Claims 12-14 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the

claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether the whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The claims recite "isolated polynucleotide encoding a carboxylesterase capable of the cleavage of an ester or carbamate linkage of a chemotherapeutic prodrug." The genus of carboxylesterase and chemotherapeutic prodrug potentially encompass a large number of enzymes and prodrugs. Especially chemotherapeutic prodrug according to the definition of the specification, it encompasses any chemotherapeutic agent that can be metabolized in vivo. The specification only discloses a rabbit carboxylesterase that is capable of cleaving the ester linkage of chemotherapeutic agent CPT-11 and its inactive metabolite APC. The specification fails to disclose other carboxylesterases that works in these agents. The specification fails to teach what biochemical or physical properties these carboxylesterase must share to have this function. In addition, the specification fails to disclose other types of chemotherapeutic prodrugs that can be cleaved to active metabolites in vivo. The specification neither describes a representative number of species by their complete structure nor their other relevant identifying characteristics. Therefore, the specification fails to describe the invention in such a way to reasonably convey one skilled in the art that the inventors had possession of the invention at the time the application was filed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
April 4, 2003

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER